UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,658	04/19/2001	Allan Bradley	S2037-700210	9914

37462 7590 11/15/2007

LOWRIE, LANDO & ANASTASI
RIVERFRONT OFFICE
ONE MAIN STREET, ELEVENTH FLOOR
CAMBRIDGE, MA 02142

EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
11/15/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@ll-a.com
gengelson@ll-a.com

Office Action Summary	Application No.	Applicant(s)	
	09/839,658	BRADLEY ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17,67,68 and 72-94* is/are pending in the application.

4a) Of the above claim(s) *73-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17,67,68 and 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 10, 2007 has been entered.

2. Claims 1-14, 17, 67, 68 and 72 were previously pending. Applicants added new claims 73-94, therefore claims 1-14, 17, 67, 68 and 72-94 are pending.

3. Newly submitted claims 73-94 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 73-85 correspond to originally filed claims 54-60, which were restricted into a separate group in the Election/Restriction Requirement dated May 31, 2002. Further, the newly presented claims 86-94 are drawn to a kit for hybridization under controlled humidity and with the use of antioxidant, again, subject matters not originally elected by Applicants for examination.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 73-94 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 1-14, 17, 67, 68 and 72 will be examined.

5. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of

record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Interpretation

6. Applicants did not define the term "about X bases", therefore, for example, the term "about 30 bases" is interpreted as any number of bases between one and 100, for example. In addition, the phrase "greater than about X bases" is interpreted as any number of bases, as are phrases "smaller than about X bases" and "no more than about X bases".

7. With respect to the term "stringent hybridization conditions", Applicants provided the following description (page 13, lines 14-19 and 29-31; page 14, line 1):

"...The term "stringent conditions" refers to conditions under which a probe will hybridize preferentially to its target subsequence, and to a lesser extent to, or not at all to, other sequences. A "stringent hybridization" and "stringent hybridization wash conditions" in the context of nucleic

acid hybridization (e.g., as in array, Southern or Northern hybridizations) are sequence dependent, and are different under different environmental parameters." And

"...However, the selection of a hybridization format is not critical, as is known in the art, it is the stringency of the wash conditions that set forth the conditions which determine whether a nucleic acid is within the scope of the invention."

Therefore, depending on the length of the nucleic acids participating in the hybridization reaction, different conditions will be considered as being "stringent".

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-6, 12-14, 17, 67, 68 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96; cited in the previous office action), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993; cited in the previous office action).

A) Regarding claim 1, Kallioniemi et al. teach detection gene copy number amplifications or deletions by hybridization of target nucleic acids to an array of plurality of immobilized probes by the method comprising:

(a) providing the plurality of nucleic acid probes comprising a plurality of immobilized nucleic acid segments in an array with each probe at a known location, wherein each probe is a

member of a genomic library cloned in a vector, and each probe is the vector having a cloned nucleic acid insert greater than 50 kilobases, wherein the plurality of probes represents all of the chromosome or a genome (Kallioniemi et al. teach CGH (comparative genomic hybridization) arrays (page 2, [0013], [0022]), and DNA arrays in which large-insert genomic clones such as P1, BAC or PAC clones (= probes) are attached to solid support (page 3, 4 [0053]). Kallioniemi et al. teach an array of clones representing all of the human genome (page 14, [0152], [0153]). Kallioniemi et al. teach an array of P1, BAC or PAC clones each of which has an insert of 80 to 150 kilobases (page 15, [0156]). Kallioniemi et al. teach an array of clones at known locations (Fig. 14).);

(b) contacting the immobilized probes with a sample of target nucleic acid comprising fragments of genomic nucleic acid, wherein said fragments include both strands of a double-stranded genomic DNA fragment and include at least 30% repetitive sequences, and wherein both strands are labeled with a detectable moiety, wherein each labeled fragment consists of a length smaller than 200 bases, and the contacting is under conditions allowing specific hybridization of both strands of the labeled fragment of the target nucleic acid to the probe nucleic acid (Kallioniemi et al. teach contacting genomic DNA target labeled with a fluorescent dye (= detectable moiety) to a CGH array (page 14, [0152]). The target DNA is contacted with the immobilized probes under conditions which permitted specific hybridization of the target to the probes (page 2, [0016]). Kallioniemi et al. teach human genome (page 14, [0153]). Therefore, since human genome contains at least 30% of repetitive sequences, by teaching human genome Kallioniemi et al. inherently anticipate this limitation.); and

(c) observing an amount and location of labeled genomic nucleic acid hybridized to each immobilized probe, to detect regions of amplification or deletion in the sample, wherein positional

information of clones on the arrays and chromosomes is correlated, thereby generating a molecular profile of the chromosome or genome of the sample genomic nucleic acid (Kallioniemi et al. teach observation of hybridization events using a CCD camera and detection gene amplifications or deletions on chromosomes (page 2, [0013], [0016]; page 15 [0157], [0160]).).

Regarding claims 12 and 13, Kallioniemi et al. teach hybridization conditions of 42° C and wash of 55° C (page 8, 9, [0100], therefore, according to Applicants' description, they teach stringent hybridization conditions and temperature about 60° C.

Regarding claim 14, Kallioniemi et al. teach target nucleic acid consisting of human DNA (page 14, [0152]).

Regarding claim 17, Kallioniemi et al. teach human genome (page 14, [0153]).

Regarding claims 67 and 72, Kallioniemi et al. teach the sample nucleic acid being chromosome 22 (page 10, [0116]).

Regarding claims 68 and 72, Kallioniemi et al. teach the sample nucleic acid being total human DNA, therefore anticipating the limitations of a sample comprising at least one chromosome and a sample comprising a complete genome (page 14, [0152]; page 15, [0156]).

B) Kallioniemi et al. do not teach DNA fragments with length of less than about 200 bp to less than about 30 bp.

C) Regarding claims 1-6, 70 and 71, McGill et al. teach detection of chromosome 8 (= probe) amplification using probes (= target nucleic acid fragments) derived from the chromosome (col. 3, lines 56-67; col. 4, lines 16). The probe lengths were 10-500 bp (col. 5, lines 35-45 and 52-55), with the optimal probe sequence being about 20 bases (col. 6, lines 1-10). Therefore, since the probes of McGill et al. are shorter than 200 bp, the result of using them in hybridization would be less probe aggregation and lower hybridization background, since each of the probes would anneal

to a 20 bp sequence which appears once in 4^{20} bp in the genome, or once every 1,099,511,627,776 bp in the genome (as compared to human genome size of 3,000,000,000 bp), that binding of such probes will be very specific, therefore reducing background and non-specific aggregation.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used short target fragments of McGill et al. in the hybridization method of Kallioniemi et al. The motivation to do so, provided by McGill et al., would have been that fragments with about 20 bases allow formation of duplexes which are stable and selective (col. 6, lines 1-3).

Additional motivation for using short fragments in hybridization is provided by Pollack et al., who teach hybridization of DpnII digested and labeled genomic DNAs to cDNA arrays (Abstract; page 46, first paragraph). They found that reducing the size of genomic DNA before labeling improved labeling efficiency by providing greater accessibility of the DNA template following digestion. Such greater accessibility would also allow more specific annealing of the probes to the array.

D) Neither Kallioniemi et al. nor McGill et al. specifically teach double-stranded DNA fragments labeled on both strands.

E) Pollack et al. teach labeling of genomic DNA digested with DpnII and labeling the genomic DNA with a BioPrime labeling kit from GibcoBRL (page 46, first paragraph) for hybridization to a cDNA array. As evidenced by the GibcoBRL catalog, the BioPrime labeling kit contains a DNA polymerase and random primers (page 18-16), therefore, the labeling reaction would result in amplified double-stranded DNA with both strands labeled.

It would have been *prima facie* obvious to have used the BioPrime labeling kit of GibcoBRL to produce double-stranded labeled DNA fragments in the method of Kallioniemi et al., McGill et

al. and Pollack et al. The motivation to do so is provided by Mackey et al., who teach using the BioPrime kit to label genomic DNA to create probes for hybridization, and teach that probes were prepared from as little as 1 ng of starting material (Abstract), and, as stated by Mackey et al. (page 434, last paragraph):

"In summary, the random primer biotin labeling system described here has a number of attractive features. Small amounts of template DNA (as little as 1 ng) can be amplified and labeled resulting in hundreds of nanograms to microgram of biotinylated probe. This amplification method is especially useful for labeling of DNAs which are difficult to isolate in large quantities; these include YACs, cosmids and DNA isolated from agarose and polyacrylamide gels. The probe size is small and and is suitable for in situ hybridization procedures."

10. Claims 7, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action) and Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96; cited in the previous office action), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993; cited in the previous office action), as applied to claim 1 above, and further in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action).

A) Regarding claim 7, Kallioniemi et al. teach generation of nucleic acids by polymerase chain reaction, nick translation or random priming (page 10, [0114]-[0116].

Regarding claim 8, Kallioniemi et al. teach labeling of nucleic acid fragments by nick translation or random priming (page 10, [0116]).

B) Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. do not teach fractionation of DNA by DNAse digestion.

C) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNAse I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used DNAse I digestion of Anderson to fragment genomic target DNA in the method of Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by Anderson, would have been that DNAse I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNAse I in the reaction (page 3019, first two paragraphs).

11. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96; cited in the previous office action), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993; cited in the previous office action), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action), as applied to claim 8 above, and further in view of Waggoner et al. (U. S. Patent No. 5,268,486; cited in the previous office action).

A) Claim 9 is drawn to the label comprising Cy3 or Cy5.

B) Kallioniemi et al. and McGill et al. teach fluorescent labels, but do not teach Cy3 or Cy5.

C) Waggoner et al. teach luminescent cyanine dyes, including Cy3 and Cy 5 (col. 19, formula at the bottom; claim 8; Cy3 has m=1, Cy5 has m=2). The dyes are be used to label nucleic acids (col. 2, lines 58-61; col. 4, lines 29-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the cyanine dyes of Waggoner et al. in the method of Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by Waggoner et al., would have been that cyanine dyes were used for detecting mixtures of components because they had a wide range of excitation and emission wavelengths (col. 4, lines 36-49).

12. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96; cited in the previous office action), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993; cited in the previous office action), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action), as applied to claim 1 above, and further in view of Ordahl et al. (Nucl. Acids Res., vol. 3, pp. 2985-2999, 1976; cited in the previous office action) and Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1981; cited in the previous office action).

A) Claim 11 is drawn to fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNAse digestion.

B) Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. do not teach fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNAse digestion.

C) Ordahl et al. teach fragmentation of genomic DNA in preparation for DNA hybridization experiments. Ordahl et al. teach that it is advantageous to use DNA fragments of less than 500 bp in hybridization experiments (page 2985, first paragraph). Ordahl et al. teach that DNA fragmented

in French press had an average size of 230 base pairs (Abstract; page 2986; Fig. 4). Ordahl et al. do not teach DNAse I fragmentation after shearing.

D) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNAse I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used shearing of Ordahl et al. and DNAse I digestion of Anderson to fragment genomic target DNA in the method of Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by Ordahl et al. and Anderson, would have been that it was advantageous to use short DNA fragments in hybridization (Ordahl, p. 2885, first paragraph) and that DNAse I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNAse I in the reaction (Anderson, page 3019, first two paragraphs).

13. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
11/8/07